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Hypoxia in the Eye: A Two-Sided Coin

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Abstract

Grimm, Christian, Gabriel Willman. Hypoxia in the eye: A two-sided coin. *High Alt Med Biol.* 13:169—175, 2012.—Tissue oxygenation in general and hypoxia in particular are important regulators of retinal physiology and pathophysiology. Reduced oxygen tension and hypoxia-inducible transcription factors along with some of their target genes are critically involved in retinal development, and especially in the generation of a normal retinal vasculature. Well-timed hypoxia is thus vital for the young eye to establish proper retinal function and vision. However, when hypoxia is ill-timed, reduced oxygen tension may be associated with the development of retinal pathologies, including retinopathy of prematurity, diabetic retinopathy, glaucoma, age-related macular degeneration, or high altitude retinopathy. Here, reduced oxygen tension activates a hypoxic response that culminates in an increased expression of vascular endothelial growth factor. This causes pathological neovascularization of the delicate neuronal retina, a process that may ultimately lead to loss of vision. In contrast, preconditioning by well-defined and controlled short-term hypoxia is not devastating for the retina but instead induces a molecular response that provides protection to neuronal cells. Detailed investigation of hypoxic mechanisms during development and adulthood may thus reveal factors, which may be targeted by therapeutic approaches to save and preserve vision in patients.

Key Words: hypoxia inducible factor, erythropoietin, ophthalmic changes

Introduction

Visible light has to reach the light-sensitive photoreceptors in the retina efficiently and with minimal scattering to ensure maximal sensitivity and visual acuity. Thus, cornea, lens, and vitreous are clear and avascular structures that allow maximal penetrance for those wavelengths of light useful to the visual system. Although these structures do not contain blood vessels in the adult eye, oxygen is nevertheless an important regulator of their physiology. Insufficient oxygenation of the cornea, for example, has been associated with pathological vascularization influencing tissue integrity and visual acuity (Safvati et al., 2009). Increased oxygenation of the lens, on the other hand, may reduce lens clarity and thus sensitivity of the visual system (McNulty et al., 2004). Although control of oxygenation in these tissues is of high importance for the process of vision, this review will focus on the significance of fine-tuned oxygen levels for the retina during development and in the adult eye. Disturbed oxygenation is associated with the pathology of several blinding diseases of the retina (Fig. 1A–1D), and may also impact on retinal function and tissue integrity at high altitudes.

Hypoxia in Retinal Pathologies: The Bad Side of the Coin

High altitude-associated changes

Reduced oxygen levels at high altitude correlate with several retinal changes in human subjects. Studies in mountaineers revealed that an ascent to high altitude may cause morphological and functional changes of the retina, such as optic disc swelling, changes of macular function including color discrimination, altered retinal and choroidal blood flow, and retinal hemorrhages (Frayser et al., 1970; Wiedman, 1975; Pavlidis et al., 2005; Morris et al., 2007; Bosch et al., 2008, 2009; Willmann et al., 2010, 2011; Ho et al., 2011; Fischer et al., 2012). While some of these changes present physiological adaptive mechanisms to high altitude exposure such as increased blood flow and increased tortuosity of blood vessels, others present potentially pathological changes to hypoxia, such as optic disc swelling or retinal hemorrhages. Interestingly, a significant portion of high altitude mountaineers develop detectable retinal hemorrhages only after their return to base camp from very high altitudes (Barthelmes et al., 2011). However, most of the observed changes are reversible with time, suggesting that

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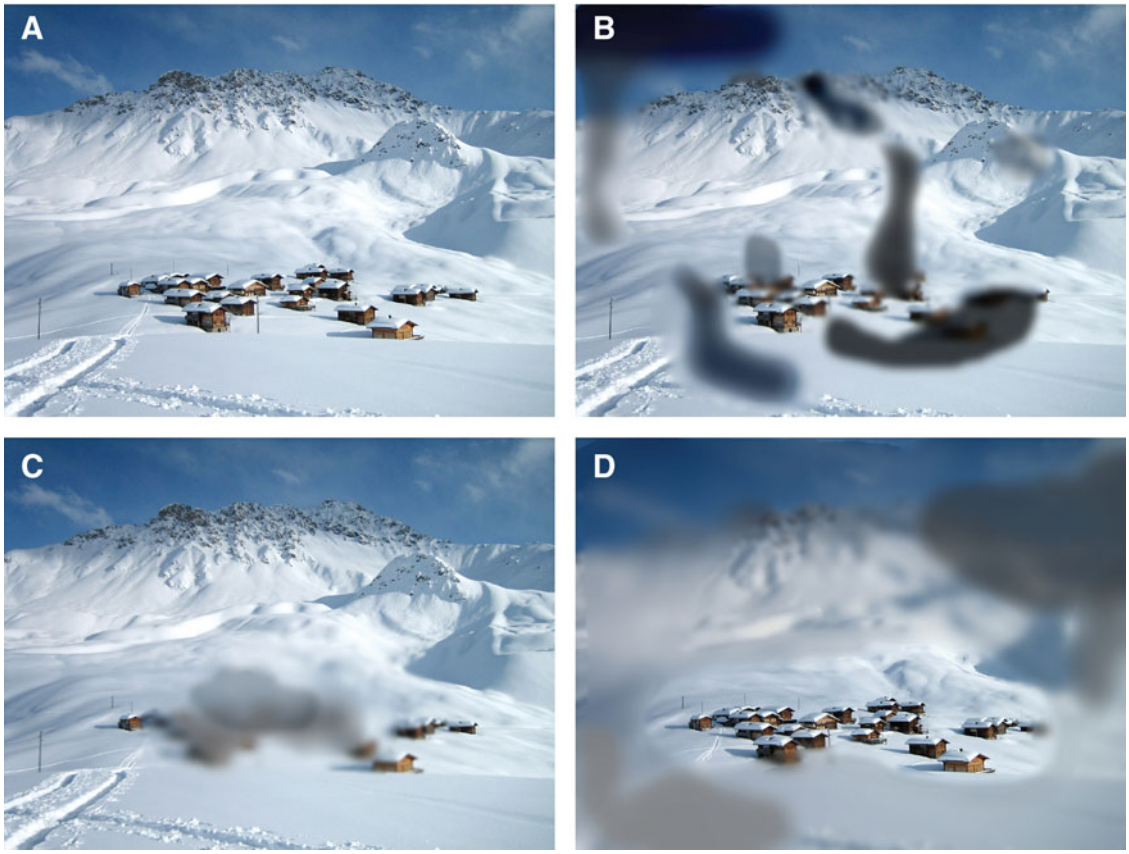

FIG. 1. The mountain village Medergen (Switzerland, 2000 meters above sea level) as seen by a person with normal eyesight **(A)**, and by patients affected by diabetic retinopathy **(B)**, age-related macular degeneration **(C)**, or glaucoma **(D)**.

the normal retina has an intrinsically protective system that has the capacity to cope with and adapt to transient changes in oxygen levels. However, this system may not be sufficient to protect retinal integrity and function in all situations. Especially if hypoxia lasts for an extended period of time, or if hypoxia occurs in the presence of additional stress factors such as certain gene mutations and pre-existing systemic or ocular disease, changing oxygen levels may be devastating for the retina and thus for visual function in human patients. It is clear, for example, that reduced tissue oxygenation negatively influences retinopathy of prematurity (ROP), diabetic retinopathy (DR), age-related macular degeneration (AMD), and glaucoma.

Retinopathy of prematurity

Changes in retinal oxygenation in preterm infants are associated with ROP, which accounts for 6% to 18% of visual impairment in children (Gilbert et al., 1997). After birth, newborns experience oxygen levels that are hyperoxic relative to the *in utero* situation (Mintz-Hittner and Best, 2009). The retinas of children born at term tolerate this sudden change in oxygenation since the retinal vasculature is already fully developed. In infants born prematurely, however, the relative hyperoxic environment may reduce production of hypoxia-related pro-angiogenic factors and prevent complete maturation of the retinal vasculature, or even cause vessel dropout. Relative tissue hypoxia, which may follow this hyperoxic phase as soon as retinal cells start to function, is thought to be then responsible for abnormal vessel growth leading to neovascularization, and eventually to scarring, formation of hemorrhages, and/or retinal detachment (Mintz-Hittner and Best, 2009). The molecular response to this second phase of ROP centers around activation of hypoxia-inducible transcription factors (HIFs), which regulate expression of various genes important for vessel growth such as vascular endothelial growth factor (VEGF), erythropoietin (EPO), and others (Lee et al., 2004). Although local anti-VEGF therapy may significantly improve disease outcome, future approaches to further increase efficacy of treatment may need to target additional pro- or inhibitory angiogenic factors (Table 1), or upstream mechanisms regulating expression of these factors. Controlled destabilization of HIFA subunits, for example, might be a possible way to simultaneously influence expression of most genes regulating neovascular vessel growth, and may thus have a larger inhibitory impact on disease progression.

Nevertheless, until today the mainstay of ROP treatment remains laser therapy, while the off-label use of anti-VEGF antibodies has only been shown to be superior compared to laser treatment in ROP zone I. Advantages of anti-VEGF antibodies include the potential induction of neovascular regression, as well as the development of a more physiological vasculature (Mintz-Hittner and Kuffel, 2008; Stahl et al., 2011).

Diabetic retinopathy

DR affects a large percentage of patients suffering from diabetes mellitus. Symptoms include blurred vision, shadows

Table 1. Selected Key Angiogenic Factors and Inhibitors in the Retina

Factor	*Name*	*Activity*	*Reference*
VEGF	vascular endothelial growth factor	pro-angiogenic	(Witmer et al., 2003)
EPO	erythropoietin	pro-angiogenic	(Watanabe et al., 2005)
IGF1	insulin-like growth factor 1	pro-angiogenic	(Simo et al., 2006)
PGF	placental growth factor	pro-angiogenic	(Carmeliet et al., 2001)
PDGF	platelet derived growth factor	pro-angiogenic	(Simo et al., 2006)
SDF	stromal-cell derived factor	pro-angiogenic	(Lima e Silva et al., 2007)
HGF	hepatocyte growth factor	pro-angiogenic	(Colombo et al., 2007)
ANG2	angiopoietin 2	pro-angiogenic	(Hackett et al., 2002)
bFGF	basic fibroblast growth factor	pro-angiogenic	(Wong et al., 2001)
CTGF	conecting tissue growth factor	pro-angiogenic	(Kuiper et al., 2004)
TGF	transforming growth factor	pro-angiogenic	(Spranger et al., 1999)
ANP	atrial natrium peptide	pro-angiogenic	(Lara-Castillo et al., 2009)
Angiostatin	angiostatin	inhibitory	(Spranger et al., 2000)
Endostatin	endostatin	inhibitory	(Noma et al., 2002)
TSP-1	thrombospondin	inhibitory	(Sargiannidou et al., 2001)

and/or missing areas of vision (Fig. 1B), retinal detachments, vitreous hemorrhages, and more. Diabetic retinopathy is a micro-angiopathy and among the most frequent causes for severe visual impairment in industrialized nations (Ferris et al., 1999; Kocur and Resnikoff, 2002). The initial phase of DR is characterized by microvascular occlusion initiated by hyperglycemia. This results in capillary nonperfusion, followed by retinal hypoxia, which leads to arteriovenous shunts characterized by vessel dropout and later by neovascularization. Clinical lesions often found in background diabetic retinopathy include micro-aneurysms with leakage or occlusion, retinal hemorrhages, macular edema, and hard exudates. The primary feature of the proliferative phase of the disease is neovascularization caused by extensive retinal hypoxia, with neovascularization being the result of an interaction between various pro-angiogenic factors with angiogenic inhibitors (Table 1) (Frank, 2004; Antonetti et al., 2012). It is important to note that stimulation or inhibition by these factors largely depends on the disease state. However, since VEGF plays a key role in disease development, novel anti-VEGF therapeutic strategies are now able to fulfill the previously unmet medical need for a treatment, which is superior to traditional laser photocoagulation for diabetic macular edema, for example (Bandello et al., 2012).

Although not fully elucidated, alterations in retinal hemodynamics with reduced blood flow in the retina may be an important factor in addition to hyperglycemia for the initiation of DR. Local or global changes in retinal oxygenation may cause the development of hypoxic areas as the disease progresses (Arden and Sivaprasad, 2011). As in ROP, activation of HIF transcription factors may then be responsible for the production of angiogenic proteins and thus for the development of a neovascular response.

Age-related macular degeneration

AMD is characterized by distorted, blurred, and reduced central vision (Fig. 1C). Affected individuals have difficulties reading, watching television, and recognizing people's faces. AMD is the leading cause of visual impairment and blindness in elderlies in the developed world (Gehrs et al., 2006). In general, AMD can be of the dry or of the wet form. In the dry form, also called geographic atrophy, retinal pigment epithelial (RPE) cells and photoreceptors in the central retina covering the macula degenerate, leading to loss of central high acuity vision. The wet form, which may or may not follow the dry form, is characterized by neovascularization of the retina with vessels originating from the choroid penetrating the RPE and growing into the neuronal retina. As in DR, alterations in ocular blood flow and hemodynamics, as well as reduced perfusion of the choriocapillaries, have been described. In addition, thickening of Bruch's membrane, alterations of RPE cells with the accumulation of lipofuscin, and the formation of drusen may reduce diffusion of oxygen from the choroid to the retina (Schlingemann, 2004; Terman and Brunk, 2004). This may lead to reduced oxygen tension causing the activation of a hypoxic response, which may lead to the development of neovascular complications. In this response, HIF factors may again be the driving force controlling initiation and progression of the devastating vessel growth (Inoue et al., 2007; Sheridan et al., 2009). The main pro-angiogenic factor in wet AMD seems to be VEGF. Anti-VEGF therapies successfully slow or even prevent neovascularization in AMD patients. Targeting HIF1 prevented production of VEGF in RPE cells *in vitro* and reduced neovascular vessel growth in animal models *in vivo* (Zhang et al., 2007, 2010; Yoshida et al., 2010), suggesting that hypoxia-induced HIF1 might be responsible for the development of wet AMD and loss of vision.

Glaucoma

Glaucoma is the second leading cause of blindness worldwide (Quigley and Broman, 2006). The death of retinal ganglion cells in glaucoma may disconnect the retina from the visual cortex, preventing signal transmission and formation of useful vision in patients. Patients may initially experience blurred and cloudy vision, especially in the periphery (Fig. 1D). If untreated, glaucoma may lead to complete blindness. Vascular abnormalities and altered blood flow at the optic nerve head may lead to local hypoxia, accelerating neuronal cell death in patients (Osborne et al., 2001; Flammer et al., 2002). Again, HIF1 is thought to be involved in the pathology of glaucoma: increased presence of HIF1A was found in glaucomatous eyes and localization of this protein correlated with regions of visual field defects (Tezel and Wax, 2004).

Hypoxia in Retinal Development: The Good Side of the Coin

Cells of the retina may experience a period of relative hypoxia before the capillary network in the vascular plexi is established and functional. This has mostly been investigated in mice and rats in which final retinal and vascular development occurs postnatally. At birth, the mouse retina is avascular and three vascular plexi develop from the optic nerve head in a radial fashion within the first 2 weeks of life. Local hypoxia may control production of VEGF, which is essential for the primary vascular plexus in the nerve fiber layer to develop. VEGF is thought to be primarily produced by astrocytes (West et al., 2005), but ganglion cells (Sapieha et al., 2008) may also contribute to the formation of a VEGF gradient with highest concentrations in the initially avascular peripheral retina (Stone et al., 1995). Although VEGF may be most important for development of the primary vascular plexus, factors such as insulin-growth factor 1, placental growth factor, leukemia inhibitory factor, and others play a role as well (Caprara and Grimm, 2012). Similar to the formation of the primary plexus, hypoxia-driven expression of VEGF seems crucial for angiogenic sprouting preceding formation of the deeper plexi. For this step of vascular development, VEGF is expressed by cells of the inner nuclear layer, presumably by Muller glia cells (Stone et al., 1995). Developmental hypoxia and VEGF expression has also been described for the primate retina (Sandercoe et al., 2003), suggesting that the mechanisms governing retinal vascular development might be well conserved.

Since expression of VEGF is mainly controlled by HIF transcription factors, HIFs might be strongly involved in the regulation of the vasculature in the retina. Furthermore, it has been suggested that developmental hypoxia may also participate in controlling the number of retinal neurons through regulating the physiological process of developmental apoptosis or programmed cell death (Maslim et al., 1997; Mervin and Stone, 2002). Thus, it seems important that oxygen levels are kept within a physiological range to ensure proper spatial and timely activation of HIFs and their downstream target genes, especially during development of the retina. Disturbing this fine-tuned system may profoundly influence retinal architecture and thus the functional performance of the tissue with strong consequences for vision. It may therefore not be surprising that mice with a conditional knockout of *Hif1a* in most cells of the peripheral retina do not develop a normal retinal vasculature. In the absence of HIF1A protein, the intermediate vascular plexus does not form, whereas the primary and the deep plexi are less affected. The architecture and cellular composition of the neuronal retina, however, seems normal. Interestingly, lack of HIF1A leads to an increased expression and activation of HIF2A, probably as a compensatory reaction. As a consequence, *Epo* levels are strongly elevated in these mice (Caprara et al., 2011).

Not only a reduced (lack of HIF1A), but also an overstimulated hypoxic response disturbs retinal development. Von Hippel Lindau (VHL) protein is a main factor in the degradation of HIFA proteins in normoxic conditions. Lack of VHL leads to the stabilization and functional activation of HIF1 and HIF2, even at normal oxygen levels (Haase et al., 2001). Deletion of *Vhl* in the developing retina generates a sustained and misregulated hypoxia-like molecular response with the activation of HIF1 and HIF2. This leads to severe consequences for the retinal vasculature and the neuronal tissue. The embryonic vasculature in the vitreous does not regress and the retinal vasculature does not develop correctly (Kurihara et al., 2010; Lange et al., 2011a). Vascular plexi are severely disturbed and vessels penetrate all cell layers, including the photoreceptor layer. Mis-regulated angiogenic factors include *Vegf*, *Epo,* and others. Since exogenous application of a VEGF receptor (FLT1) that binds and inactivates VEGF prevents most of these changes, mis-expression of HIF-controlled VEGF seems responsible for the observed alterations. This is further supported by the rescue of the phenotype by HIF1 ablation (Kurihara et al., 2010). The vascular abnormalities also induce severe retinal degeneration with loss of most neurons, leading to a strong reduction in retinal function and thus in vision (Lange et al., 2011a).

In conclusion, physiological hypoxia is required for proper development of the retinal vasculature and tissue architecture. Only if the hypoxic response system can react properly to changes in tissue oxygenation, the retina will develop into a mature, well-structured, and functional organ. Thus, physiological hypoxia is a critical environmental clue and is essential for the formation of a functional visual system. That it is this hypoxic clue and not only an intrinsically activated genetic program that regulates development of the vasculature is established with experiments involving exposure of newborn mice to hyperoxia to prevent formation of physiological tissue hypoxia. This treatment prevents activation of HIF transcription factors, demonstrating that their normal developmental activation is not due to a developmental program initiated at specified time points after birth, but rather to alterations in tissue oxygenation. Hyperoxia not only prevents HIF activation but also arrests the formation of retinal blood vessels and even leads to vessel dropout in wild type mice. Reactivation of the HIF system after reduction of oxygen levels leads to neovascular changes and loss of neuronal cells (Smith et al., 1994). Such experiments clearly demonstrate that hypoxia provides important environmental signaling cues that are vital for retinal physiology and function.

Hypoxia in Retinal Neuroprotection: Another Good Side of the Coin

Although long-lasting hypoxia is devastating and may lead to retinal degeneration and loss of vision (see above), short-term hypoxic exposure can precondition the tissue and prepare it to cope with a subsequent toxic insult. Cells and animals can be preconditioned by a temporary reduction of oxygen concentrations in the cell culture medium or breathing air, respectively. It has been shown that preconditioning of mice protects the retina against ischemic-reperfusion injury (Roth et al., 1998), and against degeneration of photoreceptors after exposure to bright light (Grimm et al., 2002). The underlying molecular mechanisms are unclear but locally produced EPO may be part of the protection. Recombinant EPO delivered by local or systemic injections, or by viral-mediated gene transfer can provide partial protection for photoreceptors in some but not all situations (Grimm et al., 2002, 2004; Rex et al., 2004, 2009). This may suggest that neuroprotective factors in addition to EPO are produced during or after the period of hypoxic preconditioning. The identification of those factors might provide the basis for an efficient therapeutic approach to treat human patients suffering from retinal degeneration. Due to the short-lived effect of hypoxic pre-

conditioning, it is not possible to test whether the treatment would also protect against slower degenerations induced by gene mutations. It is also not clear whether the combination of factors induced by hypoxic preconditioning would be capable to protect cells in all situations. Erythropoietin alone at least is not. Constitutive overexpression of *Epo* provides some protection against light damage but not against degeneration induced by a mutation in rod opsin or a mutation in rod phosophdiesterase (Grimm et al., 2004). Direct application of EPO or systemic expression of *Epo* from a virally transferred gene, however, protects photoreceptors in the presence of a mutation in the peripherin gene (Rex et al., 2009; Sullivan et al., 2011).

Analysis of the retinal transcriptome showed that hypoxic preconditioning differentially regulates a large number of genes, but factors responsible for protection have not yet been defined (Thiersch et al., 2008). It seems clear, however, that expression of HIF1-regulated genes in photoreceptors is not essential for autocrine protection (Thiersch et al., 2009), suggesting either that protective factors are produced by other classes of retinal cells to act *in trans* on photoreceptors, or that factors controlled by HIF2 (or by other transcription factors differentially regulated by hypoxia) are needed by photoreceptors to survive light exposure. Possibly, full protection is only achieved if both autocrine and paracrine factors are acting together. Deletion of VHL from rod photoreceptor cells induces a hypoxia-like response in normoxia with the activation of HIF1, HIF2, and STAT3, and protects photoreceptors from light damage. However, protection is only transient (Lange et al., 2011b), again arguing that a hypoxic response restricted to photoreceptors participates in the protection but is not sufficient for full protection.

The response to reduced oxygen tension may not be solely determined by the stabilization of HIF transcription factors. Increasing evidence suggests that epigenetic mechanisms may also be involved in the regulation of HIF-mediated gene transcription. Retinas tolerating ischemia contained increased levels of trimethylated histone H3 and mono-ubiquitinated histone H2A (Stowell et al., 2010), both of which are implicated in epigenetic transcriptional regulation (Bantignies and Cavalli, 2006). In addition, DNase-1 hypersensitive areas obviously allow facilitated binding of HIF transcription factors to their respective binding sites in promoters of target genes (Schodel et al., 2011), suggesting that epigenetic mechanisms are important regulators of the hypoxic response in a variety of situations.

Conclusions and Outlook

The retina is one of the most metabolically active tissues of the body. Photoreceptor cells consume up to 10^8 ATP molecules per second in darkness (Okawa et al., 2008), and cells of the RPE are among the most active phagocytes of the body (Reme, 2000). Thus, proper function of the adult retina requires that cells are sufficiently supplied with nutrients and oxygen. Any alterations in oxygenation levels may have devastating consequences for vision if no adequate cellular or tissue response can be activated to cope with the condition. Understanding how such a response is regulated on a molecular level may not only increase our knowledge about fundamental biological processes during development, maturation, and aging, but may also reveal new targets for the treatment of sight-frightening diseases in human patients. Factors in the HIF-activation pathway, HIF target genes and/or proteins regulating tissue oxygenation itself may provide a number of possibilities to support retinal cells and to maintain normal retinal physiology and function.

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